

Remifentanil for obstetric analgesia and anesthesia : a review of the literature

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INTRODUCTION

Based on theoretical grounds, remifentanil, an ultra-short acting opioid, has a favorable pharmacodynamic and pharmacokinetic profile for obstetric anesthesia/analgesia (13). When regional anesthesia is contraindicated, remifentanil is an intriguing option to provide labor analgesia using patient controlled intravenous analgesia (PCIA) (22). The rapid onset and offset would allow easy titration and feelings of self control so desired by parturients.

When general anesthesia is required for Cesarean section, remifentanil is an attractive option and possibly will be the first opioid for routine use. Maternal hemodynamic changes associated with laryngoscopy and surgical incision can easily be managed. This is especially important in high risk preeclamptic, neurologic or cardiac patients. Because of its rapid fetal redistribution and esterase metabolism, neonatal half-life is extremely short-lived (13), eliminating prolonged neonatal respiratory depression. Also during Cesarean section performed with neuraxial anesthesia, remifentanil can be useful to treat breakthrough pain. The present review will focus on these issues in more detail.

PLACENTAL TRANSFER OF REMIFENTANIL

In a landmark study, KAN *et al.* evaluated the placental transfer of remifentanil and its neonatal and maternal effects when administered as an intravenous infusion (0.1 µg/kg/min) in nineteen pregnant patients undergoing non-emergent Cesarean section with epidural anesthesia (13). The observed remifentanil umbilical vein/maternal artery (UV/MA) ratio of 0.88 ± 0.78 suggests a significant degree of placental transfer. Rapid esterase metabolism and fetal redistribution is suggested by a remifentanil umbilical artery/umbilical vein (UA/UV) ratio of 0.29 ± 0.07 . Both Apgar scores and neurologic and adaptive capacity scores demonstrated alert and vigorous newborns with minimal clinical opioid effects. In pregnant

patients, the mean maternal serum concentration was less than 50% of the concentration previously observed in non pregnant patients (6). An increased clearance, altered volume of distribution, lower plasma protein concentration and an increase in non-specific esterase activity can all account for these differences.

Albeit this study did not provide us with a full pharmacokinetic picture of remifentanil (only a single blood sample was taken at one time, i.e. delivery) and albeit the fact that only low infusion rates were administered to the mother, it demonstrated the safety of remifentanil to the fetus when administered shortly prior to delivery. Since then remifentanil has been used in various clinical obstetric settings.

LABOR ANALGESIA

In an excellent editorial, Volmanen and Alahuhta described the potential of remifentanil to be used as an iv opioid for the relief of labour pain (35). Remifentanil has an ultra-short elimination and it can be titrated to individual needs. The context sensitive half life is 3 minutes in the general population. Currently there is no evidence to indicate that elimination is prolonged in newborns or in pregnant women. In neonates, a large volume of distribution and a rapid metabolism have been demonstrated (25).

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JONES *et al.* are the first to publish their experience with remifentanyl used for IV labor analgesia in three thrombocytopenic patients (12). PCIA was administered using bolus doses of 35-75 µg (0.5-1 µg/kg) with a lock-out of 2 minutes. The infusion was stopped when full cervical dilation was reached. In one patient, one episode of excessive maternal sedation and fetal decelerations was noted. Stopping temporarily the infusion resolved this problem. Despite remifentanyl rapid onset of action, initially it proved to be difficult to provide analgesia in the early phase of a contraction owing to the inevitable delay in delivering the drug. This was overcome by the patient learning to anticipate the next contraction. Thereafter, analgesia was reported to be good. Thurlow and Waterhouse also successfully treated thrombocytopenic patients with IV PCIA remifentanyl (30). Their PCIA settings were 20 µg bolus with a lock-out of 3 minutes. Both patients were extremely pleased with analgesia. No serious adverse maternal and neonatal effects were noted. However, OLUFOLABI *et al.* reported disappointing levels of analgesia and significant side-effects (nausea, vomiting, pruritus, hypoxemia and obstructive respiration) with PCIA using a bolus of 0.125-0.5 µg/kg with a 2 minute lock-out period (19). Possibly, the fact that anesthesiologists administered remifentanyl, only starting IV administration at the onset of a contraction can explain why analgesia was insufficient. Additionally relatively low hourly remifentanyl doses were administered as compared to the two initial reports.

These initial reports were followed by more extensive single drug, open labelled studies. BLAIR *et al.* studied 21 healthy parturients (4). Remifentanyl was available in increasing bolus doses (0.25-1 µg/kg) with or without a background infusion (0.025-0.05 µg/kg/min). Lock-out was 2 minutes. In 90% of patients good analgesia was achieved and 62% of women did not require additional analgesia. Especially multiparous women were extremely satisfied with remifentanyl PCIA. Maximal levels of analgesia were already achieved without a continuous background infusion. Adverse respiratory events only occurred when a background infusion was used. Vomiting, itching and dizziness were common. It seems a continuous infusion does not provide advantages. However, OWEN *et al.* recently reported excellent and uncomplicated prolonged labor analgesia with a continuous iv remifentanyl infusion (21). Previously, ROELANTS *et al.* treated six patients with contraindications to regional anesthesia using PCIA remifen-

tanil with a background infusion (Infusion rate 0.05 µg/kg/min ; bolus dose 25 µg ; lockout period 5 minutes) (24). Good analgesia was achieved and no significant maternal or neonatal side effects were reported. VOLMANEN *et al.* evaluated 20 healthy patients and administered incremental bolus doses with a lock-out of 1 minute (34). They determined the minimum effective dose of IV remifentanyl by increasing the PCA bolus from 0.2 µg/kg with 0.2 µg/kg increments during a 60 minute study period and until a maximum of 0.8 µg/kg or the onset of significant side effects. The median effective PCA bolus was 0.4 µg/kg with a consumption of 0.066 µg/kg/min. In 10 women respiratory side effects occurred. Desaturation periods resolved spontaneously, or by breathing deeply, or by giving supplemental oxygen. The authors concluded that oxygen administration should be routine and respiratory monitoring essential.

Two randomized trials compared remifentanyl PCIA with intramuscular and IV PCA meperidine (29, 33). Volikas and Male compared remifentanyl PCIA bolus 0.5 µg/kg, lock-out 2 minutes with meperidine PCIA, bolus 10 mg, lock-out 5 minutes (33). Analgesia was superior and Apgar scores were better in the remifentanyl group. In none of the study subjects respiratory complications occurred. THURLOW *et al.* compared PCIA remifentanyl (bolus 20 µg, lock-out 3 minutes) with intramuscular meperidine (100 mg) (29). Overall pain relief was better in remifentanyl treated women, but more women experienced brief episodes of oxygen desaturation.

Currently, the analgesic efficiency of remifentanyl for labor pain has been demonstrated and it seems superior to other parenteral opioid alternatives. The optimal dose and mode of delivery need further study, but based on current knowledge a bolus between 0.2 and 0.5 µg/kg with a lockout period of 2 to 3 minutes and no background infusion seems a reasonable option. Caution remains essential and maternal respiratory monitoring mandatory as maternal desaturation and hypoventilation have been reported frequently. Further large trials are required to establish maternal and neonatal safety. We can not at the moment recommend remifentanyl for routine use in labour analgesia. However with careful monitoring and skilled personnel present at all times in the labor and delivery ward, remifentanyl is an option to treat certain patients in which more conventional options are contraindicated, as has been demonstrated by several other recent case reports (7, 8).

ANESTHESIA FOR CESAREAN SECTION

Because of the favorable pharmacokinetic profile of remifentanil in both mother and newborn, remifentanil seems an excellent opioid to be used during anesthesia for Cesarean section. During general anesthesia it could blunt the haemodynamic response associated with laryngoscopy and incision, especially in high risk patients. The rapid offset of remifentanil would eliminate the potential prolonged respiratory depressant effects associated with other opioids in neonates and parturients. It may also be useful to treat breakthrough pain or discomfort during incomplete regional anesthesia.

Sedation/analgesia during incomplete regional anesthesia for operative delivery

KAN *et al.* already demonstrated that low IV doses of remifentanil (0.1 µg/kg/min) provide mild to moderate levels of sedation in patients undergoing Cesarean section under epidural anaesthesia (13). Respiratory rate varied between 16 and 23 breaths per minute and oxygen saturation never decreased below 91%. Slight maternal respiratory acidosis was noted at blood gas analysis. Similar effects were observed by VAN DE VELDE *et al.* and MISSANT *et al.* in second trimester pregnant women undergoing fetoscopic surgery using combined spinal epidural anesthesia and remifentanil sedation (17, 32). Oxygen saturation remained within normal limits and mild respiratory acidosis was noted following repetitive blood gas analysis. Respiratory rate decreased but no periods of apnea or a respiratory rate below 8 were noted. This is in line with BABENCO *et al.* who observed mild respiratory depression following a single IV bolus of 0.5 µg/kg remifentanil in volunteers (2). Remifentanil seems a good agent to treat breakthrough pain during Cesarean section under regional anesthesia. This author uses bolus doses up to 50 µg followed by a continuous infusion at a rate of 0.1 µg/kg/min. Supplemental oxygen is administered and respiration is closely monitored as well as oxygen saturation.

Remifentanil and general anesthesia

Traditionally, general anesthesia is induced using thiopental and succinylcholine with maintenance of anesthesia, prior to delivery of the fetus, using nitrous oxide and low concentrations of inhalation agents (23). Disadvantages of this technique include maternal awareness, inadequate anal-

gesia and hypertensive responses following laryngoscopy, tracheal intubation and incision. The incidence and severity of these problems can be reduced using opioids such as alfentanil and fentanyl. However, opioids can result in low Apgar scores, neonatal respiratory depression and tracheal intubation of the newborn, as well as low neurobehavioral scores during the first days of life (1, 27). Furthermore some have expressed concern that opioids may accumulate in breast milk (28). Remifentanil, a new short acting opioid, offers similar advantages as other opioids in preventing maternal pressor responses, reducing the change for maternal awareness and reducing the risk of inadequate analgesia.

At present, 16 case reports involving 21 patients have been published in which remifentanil was given as part of a general anesthetic technique and prior to delivery of the fetus. Five of these case reports (6 patients) were in the non English literature. The remaining 11 case reports and 15 patients are listed in table 1 (3, 5, 9, 10, 11, 14, 15, 16, 20, 26, 36). Basically these case reports described the use of remifentanil as part of a general anesthetic technique in high risk obstetric patients that required general anesthesia as a result of concomitant medical disease. Especially cardiac and neurologic disease were highly prevalent in these cases. Remifentanil produced mild neonatal depression in 67% of neonates with Apgar scores less than 7 at 1 minute. At 5 minutes however the Apgar score was less than 7 in only 1 infant. Forty seven percent of newborns required brief mask ventilation.

Recently, VAN DE VELDE *et al.* performed a prospective unblinded evaluation of remifentanil in parturients requiring non-emergent Cesarean delivery under general anesthesia due to contraindications for regional anesthesia (31). Ten patients were included in this prospective case series involving 13 neonates. A bolus of remifentanil 0.5 µg/kg was given intravenously, followed by a continuous infusion at 0.2 µg/kg/min. Anesthesia was induced with propofol using target controlled infusion (TCI) set at 5 µg/ml. TCI was reduced to 2.5 µg/ml following tracheal intubation. Succinylcholine was given in a dose of 1.5 mg/kg to produce muscle relaxation and facilitate tracheal intubation. Maternal heart rate and blood pressure remained stable throughout laryngoscopy, intubation, surgical incision and surgery. One minute Apgar scores were less than 7 in 6/13 neonates. However at 5 minutes only 2 neonates had Apgar scores less than 7 and at 10 minutes Apgar scores were above 7 in all

Table 1

Neonatal outcome data as reported in 11 case reports and 15 patients in which remifentanyl was used during general anesthesia for Cesarean section

Case report	A 1 1 min	A 5 min	A 10 min	Neonatal weight (g)	Mask ventilation	Duration of mask ventilation	ETT	Naloxone	NICU
SCOTT <i>et al.</i>	6	8	8	NR	No	0	No	No	NR
BEDARD <i>et al.</i>	7	8	NR	2970	No	0	No	No	Yes
JOHANSEN <i>et al.</i>	3	5	10	635	Yes	NR	Yes	No	Yes
JOHNSTON <i>et al.</i>	8	10	NR	1960	No	0	No	No	No
MANULLANG <i>et al.</i>	6	9	NR	NR	No	0	No	No	No
McCARROLL <i>et al.</i>	6	8	NR	NR	NR	0	NR	Yes	NR
MERTENS <i>et al.</i>	3	7	9	NR	Yes	1 minute	No	No	NR
IMARENGIAYE <i>et al.</i>	6	9	NR	2830	Yes	4 minutes	No	Yes	NR
WADSWORTH <i>et al.</i>	3	9	NR	3100	Yes	6	Yes	No	Yes
WADSWORTH <i>et al.</i>	3	7	NR	2150	Yes	NR	No	No	Yes
ORME <i>et al.</i>	10	10	NR	3500	No	0	No	No	Yes
ORME <i>et al.</i>	9	10	NR	3200	No	0	No	No	No
ORME <i>et al.</i>	6	10	NR	3000	Yes	1 minute	No	No	No
ORME <i>et al.</i>	5	10	NR	2400	No	0	No	No	Yes
CARVALHO <i>et al.</i>	7	9	NR	3027	Yes	2 minutes	No	No	No

A : Apgar score ; ETT : endotracheal intubation ; NICU : admittance to neonatal intensive care unit ; NR : not reported.

Table 2

Neonatal data in 13 infants delivered from 10 patients undergoing elective Cesarean section (CS) under general anesthesia using propofol target controlled infusion and remifentanyl for induction and maintenance of anesthesia. Patient 4, 8 and 9 delivered twins.

VAN DE VELDE, *et al.*, INT. J. OBSTET. ANESTH., **13**, 153-158, 2004

	Apgar 1 min	Apgar 5 min	Apgar 10 min	Neonatal weight (g)	Mask ventilation	Duration of mask ventilation (min)	UA pH	UA pCO ₂ (mmHg)	Base excess
Patient 1	7	9	10	1250	Yes	1	7.364	50.2	2.1
Patient 2	3	6	9	1410	Yes	5	7.233	64.5	-2.6
Patient 3	7	9	9	3830	No	none	7.370	54.2	4.3
Patient 4	7	8	9	1187	No	none	7.318	52.9	-0.2
	9	9	9	1750	No	none	7.340	45.1	-1.8
Patient 5	5	9	10	3100	Yes	2	7.297	57.0	-0.3
Patient 6	5	9	10	3050	Yes	3	ND	ND	ND
Patient 7	9	9	10	3370	No	none	7.319	53.3	-1.7
Patient 8	8	9	9	1750	No	none	7.270	54.2	-3.0
	8	9	10	1650	No	none	7.300	57	-0.3
Patient 9	2	6	8	2135	Yes	3	7.322	50.1	-1.1
	4	7	8	1660	No	none	7.300	57.3	-0.2
Patient 10	1	9	9	3600	yes	2	7.205	52.8	-1.3

ND : Not done ; UA : umbilical artery.

neonates. Brief mask ventilation was required in 6 infants (Table 2).

Remifentanyl seems to be safe to the neonates, but brief neonatal respiratory depression can occur. Maternal haemodynamics remained stable. VAN DE VELDE *et al.* concluded that, "in parturients undergoing non-emergent cesarean section under general anesthesia, remifentanyl combined with propofol can be used provided adequate pediatric support is present to manage brief neonatal respiratory depression. Extrapolation of these results to a pregnancy carrying an acutely distressed fetus is premature".

CONCLUSION

Remifentanyl is an attractive short acting opioid which can be used for labor analgesia or anesthesia for Cesarean section. Especially in the latter situation it can be useful to provide maternal haemodynamic stability without prolonged neonatal depression. However, pediatric support is mandatory to manage brief episodes of respiratory depression. During labor, it can provide good levels of analgesia but close respiratory monitoring of the mother is required, making it's use cumbersome and complicated especially in smaller units.

It is however a valuable alternative if regional anesthesia is contraindicated.

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